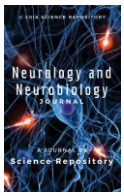

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Research Article

Is Neuraxial Clonidine a Safer Alternative to Opioids for Chronic Pain? An Alternative Worth Exploring

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ABSTRACT

Objective: Exploring the potential role of clonidine as an alternative to the currently available neuraxial medication options for the management of chronic pain.

Methods: A comprehensive literature search was conducted investigating the treatment of chronic pain using clonidine over the past 73 years. A stepwise filtering approach was used to obtain articles addressing neuraxial treatment of chronic pain in adults. Selected articles were assessed for their levels of evidence followed by a discussion of their contribution to the understanding of the role of clonidine in chronic pain management.

Results: Out of 1,035 articles that described the administration of clonidine for chronic pain management, seven articles met all of the inclusion criteria. Their levels of evidence ranged from 1a to 4 (Oxford Centre CEBM). Neuraxial administration of clonidine was found to be effective in the treatment of chronic pain, often exhibiting a synergistic effect with other analgesics to provide pain reduction with reduced opioid use. The most common side effect was hypotension, in some cases reported to have been serious.

Conclusion: The use of neuraxial clonidine, in either a primary or adjunctive role, appears promising as an effective treatment for chronic pain.

Introduction

Opioids continue to represent the medical basis in the treatment algorithm for intractable chronic pain. Yet, its common side effects play mischief with the ability to secure sustained pain relief [1]. As the prevalence of chronic pain in the United States continues to increase, advances in neuraxial medications seem necessary to expand the therapeutic algorithm for chronic pain conditions such as complex regional pain syndrome (CRPS), postherpetic neuralgia, diabetic neuropathy, cancer pain and chronic radiculopathy with or without previous back surgery [2-4].

Clonidine is an alpha-2 adrenoreceptor agonist that was initially developed as a nasal decongestant and an antihypertensive. It was subsequently found to be an effective adjuvant for the treatment of chronic neuropathic pain. When administered neuraxially, clonidine interferes with nociceptive impulses by activating the alpha-2 adrenoreceptors in the dorsal horn of the spinal cord and other sites. Early studies have demonstrated that intrathecal clonidine is effective in

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treating chronic pain, and epidural administration was found to have double the analgesic potency of intravenous administration, as well as allowing for medication dose reduction intra- and postoperatively [5-7]. Clonidine has been FDA approved in combination with opioids for the treatment of refractory cancer, shifting the opioid pain response curve to the left [8]. Obtaining the same sedation level at different time intervals of intra and postoperative analgesia and demonstrating no significant difference of reduction in heart rate and blood pressure [6]. Furthermore, achieving greater pain relief at lower doses than with either opioids or clonidine alone [8-10].

Clonidine is a promising option in the pain management paradigm with several major advantages over opioids including the lack of addiction risk. Clonidine is particularly valuable when used to treat chronic pain patients who are opioid-tolerant, opioid non-responsive, allergic to opioids or at risk for opioid addiction [8-10].

Mechanism of Action

Clonidine-induced analgesia is mediated by both alpha-2A (including cingulate alpha-2A) and alpha-2 non-A adrenoreceptors [11, 12]. Activation of these receptors leads to decreased release of norepinephrine at both central and peripheral adrenergic terminals [13]. Norepinephrine is one of the important neurotransmitters that mediates the descending inhibitory pathway in nociception [14]. Animal studies have provided evidence of the anti-nociceptive effects of clonidine. Clonidine-mediated analgesia could be due to: 1) blockade of C fiber conduction; 2) inhibition of glutamate and substance P release or increase in nitric oxide (NO) or *Gamma Aminobutyric Acid (GABA) release 3) blockade of *N-methyl-D-aspartate (NMDA) receptors activation; 4) stimulation of depolarization-induced acetylcholine release in a neuropathic state and 5) inhibition of peripheral and central neuroinflammation [15-22].

Methods

I Research Question

"What is the published evidence for safety and effectiveness of intrathecal or epidural clonidine for the management of chronic pain?"

II A Literature Review was Performed Using

i. Embase (Link; from 1974 to July 01, 2019), and
ii. Medline via PubMed (Link; from 1946 to June 27, 2019).

III Data Collection

i. Inclusion criteria: 'chronic pain', 'clonidine', 'epidural' and 'intrathecal'. No exclusion was performed according to type of study (prospective, retrospective, etc.).
ii. These studies were reviewed with regard to clinical application, dosage and route of administration, efficacy and potential side effects and complications.
iii. Articles were limited to: English language, adult, and epidural/intrathecal as route of administration.
iv. The level of evidence for each article selected for inclusion was determined based on the concept outlined by the Oxford Centre for Evidence-Based Medicine (CEBM) (Table 1).
v. Results were filtered using the stepwise approach as shown in the flowchart in (Figure 1).

Table 1: Level of Evidence by the Oxford Centre for Evidence-Based Medicine (CEBM).

Level	Therapy/Prevention, Aetiology/Harm	Prognosis	Diagnosis	Differential diagnosis / symptom prevalence study	Economic and decision analyses
1a	SR of RCTs	SR of inception cohort studies; CDR" validated in different populations	SR of Level 1 diagnostic studies; CDR" with 1b studies from different clinical centres	SR of prospective cohort studies	SR of Level 1 economic studies
1b	Individual RCT (with narrow Confidence Interval"¡)	Individual inception cohort study with > 80% follow-up; CDR" validated in a single population	Validating** cohort study with good" " " reference standards; or CDR" tested within one clinical centre	Prospective cohort study with good follow-up****	Analysis based on clinically sensible costs or alternatives; systematic review(s) of the evidence; and including multi-way sensitivity analyses
1c	All or none§	All or none case-series	Absolute SpPins and SnNouts" "	All or none case-series	Absolute better-value or worse-value analyses " " " "
2a	SR (with homogeneity*) of cohort studies	SR (with homogeneity*) of either retrospective cohort studies or untreated control groups in RCTs	SR (with homogeneity*) of Level >2 diagnostic studies	SR (with homogeneity*) of 2b and better studies	SR (with homogeneity*) of Level >2 economic studies
2b	Individual cohort study (including low quality RCT; e.g., <80% follow-up)	Retrospective cohort study or follow-up of untreated control patients in an RCT; Derivation of CDR" or validated on split-sample§§§ only	Exploratory** cohort study with good" " " reference standards; CDR" after derivation, or validated only on split-sample§§§ or databases	Retrospective cohort study, or poor follow-up	Analysis based on clinically sensible costs or alternatives; limited review(s) of the evidence, or single studies; and including multi-way sensitivity analyses

2c	"Outcomes" Research; Ecological studies	"Outcomes" Research		Ecological studies	Audit or outcomes research
3a	SR (with homogeneity*) of case-control studies		SR (with homogeneity*) of 3b and better studies	SR (with homogeneity*) of 3b and better studies	SR (with homogeneity*) of 3b and better studies
3b	Individual Case-Control Study		Non-consecutive study; or without consistently applied reference standards	Non-consecutive cohort study, or very limited population	Analysis based on limited alternatives or costs, poor quality estimates of data, but including sensitivity analyses incorporating clinically sensible variations.
4	Case-series (and poor quality cohort and case-control studies§§)	Case-series (and poor quality prognostic cohort studies***)	Case-control study, poor or non-independent reference standard	Case-series or superseded reference standards	Analysis with no sensitivity analysis
5	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"	Expert opinion without explicit critical appraisal, or based on economic theory or "first principles"

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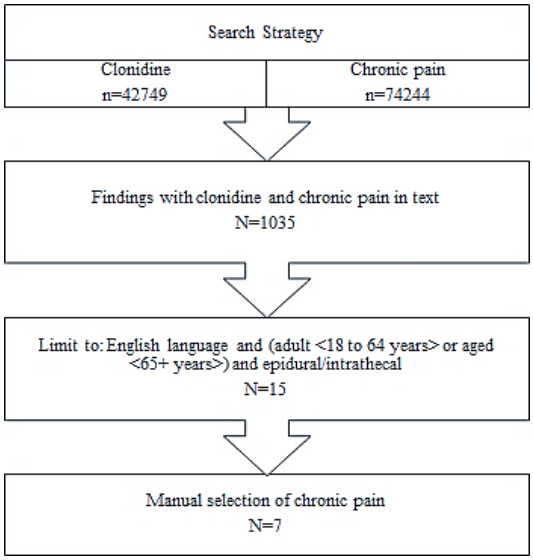

Figure 1: Flowchart of study selection process.

Results

We obtained 42749 results after selecting the following keywords for clonidine: Clonidine derivative or clonidine displacing substance or clonidine or chlorthalidone plus clonidine/ or clonidine-induced catalepsy or clonidine.mp. 74244 from chronic pain.mp. or exp chronic pain. However, subsequently a combination of the two findings 1035 findings included both terms (clonidine and chronic pain). After adding limitations for epidural and intrathecal route of administration, as well as English language and age group, we collected 15 findings. Out of these, 7 articles were included, since the remaining focused on acute pain. Table 2 summarizes each of the studies meeting the inclusion criteria and the related level of evidence for each study according to Oxford CEBM (Table 1) [23]. Five studies were randomized, controlled trials (Level 1b), one was retrospective (Level 2b), and one was a case report (Level 4).

Table 2: Summary of articles selected for inclusion from literature search.

Author	Study Design	Patient Population	N of Patients	Study Groups/Dosage	Conclusions	Level of evidence
Ackerman (2003)	Retrospective	CRPS, Neuropathic pain, Cancer pain.	15	10/15 patients with >50% pain relief on a single-dose clonidine injection(25-50 mcg), received a continuous intrathecal clonidine infusion (75-950 mcg/day) with a failure of pain relief ranging from 3-11 months.	Intrathecal clonidine is relatively safe and well tolerated, but as monotherapy did not pro-vide good pain relief in our series.	2b
Eisenach (1995)	Double-blind RCT	Neuropathic, Somatic/Visceral cancer pain	85	30 mcg/h epidural clonidine or placebo continuously for 14 days.	Successful analgesia with epidural clonidine was higher than placebo (45 vs 21%).	1b
Glynn (1996)	Double-blind, crossover	Low back and leg pain, neuropathic pain, pelvic pain and	20	Lumbar epidural clonidine (150 mcg), lidocaine (40 mg) and combination of clonidine (150	Epidural clonidine had a supra-additive effect and behaved more like a co-	1b

		Wegner's granulomatosis		mcg) and lidocaine (40 mg), all drugs were given in a volume of 3 ml.	analgesic than a pure analgesic.	
Rauck (2015)	Double-blind, crossover	Hyperalgesia and Allodynia in CRPS	22	2 groups: Intrathecal clonidine 100 mcg or adenosine 2 mg.	Intrathecal clonidine and adenosine both significantly reduced pain and areas of hyperalgesia and allodynia in patients with CRPS.	1b
Rauck (1993)	Randomized, blinded, placebo-controlled	CRPS (RSD)	26	Random order on 3 consecutive days, epidural injection of clonidine, 300 or 700 micrograms, or placebo. Patients who responded to clonidine, received continuous epidural infusion of clonidine (10 - 50 mcg/h) for 43 days.	Clonidine produced pain relief, sedation, and decreased blood pressure and heart rate after bolus epidural injection. The smaller clonidine dose (300 mcg), produced pain relief similar to those of the 700 mcg dose.	1b
Siddall (2000)	Double-blind RCT	Neuropathic pain after spinal cord injury	15	Day 1: Saline, 0.2 - 1.0 mg of morphine, or 50 - 100 mcg of clonidine. Day 2: Increased dose of the same drug (1.5 times the initial dose). Day 3: Two times the initial dose.	Intrathecal administration of a mixture of clonidine and morphine is more effective than either drug administered alone.	1b
Van Melkebeke (1995)	Case report	Neuropathic pain after arm trauma	1	Intrathecal pump: 250 mcg morphine hydrochloride and 19 mcg clonidine daily.	Patient was pain-free for over two years using the same medication dosages.	4

I Level of Evidence 1b Studies

In a study by Rauck *et al.*, 19 patients with CRPS with significant allodynia and hypersensitivity received intrathecal injections of clonidine (100 mcg) or adenosine (2 mg) in a randomized, double-blind, crossover study [24]. Each patient randomly received either a clonidine injection or an adenosine injection at the initial visit, then received an injection of the other medication at a second visit. Success was defined as a greater than 30% pain reduction on a visual analog pain score (VAS) scale within 2 hours of medication injection. Fifty-three percent (10/19) reported achieving the success criterion with clonidine, compared to 26% (5/19) with adenosine, a non-significant difference with $P = 0.20$. The pain scores for patients receiving clonidine improved significantly from pre-injection baseline to post-injection time, with significant reductions of both the area as well as the intensity of the hyperalgesia and allodynia; this effect was not seen in patients receiving adenosine. One limitation of this study was the use of a single clonidine dose level (100 mcg) instead of the evaluation of multiple dose levels. In an earlier study by the same author, 26 patients with CRPS received epidural injections of clonidine 300 mcg, 700 mcg, or saline, on subsequent days and in random order, while continuously evaluating pain with VAS [5]. Both doses of clonidine significantly reduced VAS by similar amounts within 20 minutes and pain relief lasted throughout the 6-hour monitoring period. Patients who initially responded to clonidine continued with an infusion for 43 days using a dose range of 14-50 mcg/h.

In a double-blind randomized crossover study evaluating the effects of clonidine alone or in combination with lidocaine in patients with chronic pain, clonidine was found to have a supra-additive analgesic effect. Patients received an epidural injection of clonidine (150 mcg), lidocaine (40 mg), and a combination of clonidine (150 mcg) plus lidocaine (40 mg), with a median duration of pain relief of 2, 3, and 6 hours, respectively [10]. The majority of patients who completed the three treatment arms (12 of 17) reported pain relief with the combination therapy and none reported pain relief with lidocaine alone.

In a randomized, double-blind study of 85 cancer patients having either neuropathic or somatic/visceral cancer pain despite large doses of opioids or with therapy-limiting side effects from opioids, the treatment group received a continuous epidural infusion of clonidine at a rate of 30 mcg/h for 14 days, while the control group received an epidural saline infusion. Patients were randomized after a week of epidural morphine titration phase [25]. The treatment group reported a significant reduction in pain intensity and had a higher success rate (defined as 50% or greater pain relief) than the control group (45% vs. 21%). Epidural clonidine was found to be particularly effective in patients with neuropathic pain when analysed as a subgroup. The most common side effects in the treatment group were hypotension, sedation and dry mouth and the abrupt discontinuation of clonidine led to rebound hypertension in 4 subjects, one of whom suffered a cerebrovascular accident. It should be noted that the duration of the treatment was short (14 days), and the authors did not report a continuation of pain relief for longer terms. Another important aspect is that all patients received rescue epidural morphine.

A 15-patient randomized, double-blind study was performed to evaluate the effectiveness of intrathecally administered clonidine alone, morphine alone, or a combination of morphine and clonidine to treat severe debilitating neuropathic pain after spinal cord injury [26]. First day

(saline, 0.2 - 1.0 mg of morphine, or 50 - 100 mcg of clonidine). If there was no pain relief or adverse side effects (sedation or effect on respiratory function), the subject received an increased dose of the same drug (1.5 times the initial dose) on the second day and two times the initial dose on day 3, with pain and vital signs being evaluated for 6 hours. There was nearly equal mean pain relief with either medication alone when compared to baseline (20% reduction from baseline with morphine and 17% with clonidine), and a 37% reduction with a combination of a half-dose each of morphine and clonidine. Neither medication alone resulted in greater pain reduction than saline placebo, although the mixture resulted in significant pain reduction (P = 0.0084), demonstrating a synergistic effect.

II Level of Evidence 2b Study

In a retrospective study evaluating the effectiveness of intrathecal clonidine, charts for 15 patients with CRPS, neuropathic pain and cancer pain were reviewed [27]. All patients received an initial trial of a single injection and/or a short-term infusion of clonidine, with ten patients reporting significant pain relief (>50% decrease in VAS score) and subsequently receiving a continuous long-term intrathecal infusion. Pain relief maintenance with clonidine alone varied widely from a few days until 11 months, with a daily dose of 75-950 mcg. Patients who failed clonidine alone, went on to receive a combination of intrathecally infused clonidine/opioid (Clonidine: 52-260 mcg/day; Hydromorphone: 1300-2600 mcg/day) and achieved pain relief that lasted 19-29 months.

III Level of Evidence 4 Study

In a case report of a patient with cervicobrachialgia receiving a combination of morphine (250 mcg) and clonidine (19 mcg) intrathecally daily for two years, the effect of morphine was potentiated by clonidine to achieve the desired analgesia with lower doses of morphine, demonstrating the opioid dose sparing effects of clonidine [28].

Discussion

Insufficient evidence supporting the effectiveness of opioids in the management of chronic neuropathic pain drives the need for drug alternatives [29]. The use of clonidine could avoid opioid-related complications including addiction, respiratory depression, pruritus, urinary retention, constipation, endocrine abnormalities and opioid-induced hyperalgesia. In addition, clonidine could be a potential alternative to steroids in epidural injections in vulnerable patient populations such as diabetic, hypertensive and osteoporotic [30, 31].

The analgesic effects of clonidine have been recognized and applied for over 30 years, including oral and transdermal administration for postoperative and chronic pain [32, 33]. Continuous epidural clonidine in doses of 25-50 mcg/h has been found to have beneficial effects in various study populations treated with spine instrumentation and orthopedic procedures. On the other hand, intrathecal clonidine has been administered in lesser doses of 15-40 mcg/h to avoid possible hypotension and sedation side effects with good quality evidence to support this use [34].

Efficacy

Clonidine treatment has been reported to be effective for complex regional pain syndrome (CRPS), failed back surgery syndrome (FBSS), visceral pain, cancer-related chronic pain and postherpetic neuralgia [35]. Epidural or intrathecal clonidine produces dose-dependent analgesia in patients with chronic pain. A mean reduction in pain of approximately 35% has been observed in clinical trials when using a 100-mcg dose [24]. Of interest, when opioids fail to provide significant pain relief in cases of neuropathic or mixed neuropathic-nociceptive cancer pain, additional epidural administration of clonidine has been shown to be effective in providing pain relief and may reduce the rate of opioid dose escalation [25, 36, 37]. This could be explained, in part, by the fact that alpha-2 adrenergic agonists potentiate the analgesic effects of opioids through synergism with delta receptors [28]. An important advantage of adding clonidine is reduction of the risk of opioid-induced side effects [38].

Most of the reported research into neuraxial administration of clonidine to treat chronic pain was performed over 20 years ago. Early studies utilized multiple or continuous infusion with far greater success. In a study of 26 patients with chronic reflex sympathetic dystrophy performed by Rauck *et al.*, clonidine was infused over 7 to 225 days and provided significant pain relief [5]. Glynn and O'Sullivan found that while clonidine alone provided significant pain relief in nearly a quarter of the patients treated using three separate bolus injections, three times as many patients found the best relief with a combination of clonidine and lidocaine administered in the same fashion [10]. Other researchers also found evidence that clonidine may be more effective when combined with other agents than when used alone. Eisenach *et al.* compared the use of clonidine with a saline placebo in 85 patients with severe cancer pain, all of whom were also receiving patient-controlled on-demand morphine. The authors reported successful analgesia in twice as many patients who received clonidine as for those receiving saline placebo over 14 days [25]. In a study reported by Siddall *et al.*, the combination of clonidine and morphine was found to be more effective in relieving chronic pain from spinal cord injuries in 15 patients than either medication alone [26]. Van Melkebeke *et al.* also reported the successful use of a combination of clonidine and morphine in their report on a single patient with chronic cervicobrachialgia, for which a lower dose of morphine was effective when augmented by the addition of clonidine [28].

More recently, intrathecal single bolus administration of clonidine was compared to adenosine in order to evaluate alternatives to opioids in 19 patients with CRPS. While nearly twice as many patients met the goal of >30% pain relief after receiving clonidine than adenosine, the difference was not statistically significant [24]. A significant portion of both groups did not attain the pain relief goal. The results of a study of 15 patients with either CRPS, neuropathic pain or cancer pain reported by Ackerman *et al.* also illustrate the benefit of combined medications over clonidine alone. While 10 patients reported initial pain relief with just clonidine, all 10 converted at some point to the addition of opioids to the intrathecal clonidine therapy to improve pain relief [27].

Side Effects and Complications

The reported side effects of clonidine include dose-dependent sedation or somnolence as well as hypotension, nausea, headache and dizziness [5, 24-27]. Eisenach *et al.* described six of 38 patients treated with clonidine (15.8%) as experiencing the serious adverse event of "dizziness/hypertension/hypotension" [25]. Rauck *et al.* reported that one of 20 patients (5.0%) complained of weakness in both legs following clonidine administration, although no distinct cause was found, and the weakness gradually resolved overnight [24]. It is important to note that hypotension occurs with oral and transdermal use and is consistent with clonidine's pharmacological effect. Supportive care for resulting hypotension with proper hydration is recommended. Rarely, vasopressor medications such as dopamine and norepinephrine have been used to treat severe hypotension. Other drugs including naloxone and atropine have been mentioned in the literature with inconsistent results [39]. A risk of rebound hypertension also exists following the sudden withdrawal of clonidine, such as might occur from a dislodged catheter. The potential resulting acute hypertensive crisis may require management using both alpha and beta-blockade [40, 41].

Limitations

The scarcity of clinical trials assessing neuraxial clonidine as the sole medication for pain control was the main limitation of our study. Questions such as long-term pain relief as well as comparison of clonidine alone vs. placebo are still unanswered. We observed a substantial additive effect when used in combination with other medications, especially opioids. Since there is vast evidence of pharmacological effectiveness, as well as the additive analgesic properties of clonidine, we invite the chronic pain research community to consider this medication for non-superiority and other prospective trials.

Conclusion

As documented in publications spanning decades, albeit limited in number, neuraxial clonidine could be an asset medication included in the treatment algorithm for chronic neuropathic pain. The use of clonidine could decrease or even avoid significant side effects associated with opioids including addiction, respiratory depression, pruritus, urinary retention, constipation and opioid-induced hyperalgesia. Further large and well-controlled studies are needed to substantiate the therapeutic benefits of clonidine for treatment of pain and to standardize its proper dosage for different routes of administration.

Conflicts of Interest

Nagy Mekhail: Consultant for Boston Scientific, Sollis Therapeutics, and Relievant Medsystems, Inc.; Receives research support from Mallinckrodt, Mesoblast, Halyard, and Neuros Medical; Independent medical monitor for Closed-loop SCS "Evoke study" sponsored by Saluda Medical Pty. Ltd., HF10 for PDN "Senza-PDN study" sponsored by Nevro Corp., Mild for LSS "Motion study" sponsored by Vertos Medical, and Ultra High Pulse Width SCS "Hi-Fi study" sponsored by Nuvectra Inc. Shrif Costandi: Nothing to disclose; Ali Ebd-Alsayed: Consultant for Medtronic, StimWave, Sollis and Avanos; Jijun Xu: Nothing to disclose; Lou-Anne Acevedo-Moreno: Nothing to disclose; Gregory Fiore: Employee of Sollis Therapeutics; Leonardo Kapural: Consultant for Abbott, Nalu, Biotronik, Gimer, Medtronic, Nevro; Research Grants: Saluda, Sollis, Neuros, Avanos; Christopher Gilligan: Funded Research: Sollis Therapeutics, Mainstay Medical; Consulting: Medtronic, Abbott, Saluda, Nuvectra; Ali R. Rezai: Equity position: Sollis Therapeutics and Neurotechnology Innovation Management; Board of Directors, Sollis Therapeutics.

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